or an amylin agonist alone or in conjunction with another obesity relief agent. Additionally, methods for reducing insulin-induced weight gain are disclosed which comprise administration of a therapeutically effective amount of an amylin or an amylin agonist.

On page 1, lines 4-7, replace the current paragraph in its entirety with the following:

--This application is an application filed under 35 U.S.C. ~~§ 371~~ of PCT/US98/11753, filed June 5, 1998, and is a continuation-in-part of U.S. Patent Application Serial No. 08/870,762, filed June 6, 1997, now pending.--

Please replace pages 32 thorough 34 and 37 through 39 of the specification in their entirety with the enclosed pages 32-34 and 37-39.

REMARKS

Claims 1-15 are pending and directed to methods of treating or preventing obesity in a human subject by administering an effective amount of an amylin or an amylin agonist (claims 1-10) and methods of reducing insulin-induced weight gain in human subjects using amylin or an amylin agonist (claims 11-15). A sister case bearing the same title and having serial number 08/870,762 is also pending before the Examiner.

As a preliminary matter, Applicants point out to the Examiner that a Revocation and Power of Attorney was filed in the present application on March 13, 2001, a copy of which is enclosed. Applicants request that the correspondence address be changed on all Patent and Trademark Office records for the present application. Applicants request that all future correspondence be directed to:

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I. Objections

A. Abstract

The Examiner objected to the alleged absence of an abstract as required by 37 C.F.R. 1.72(b). The application has been amended as previously suggested by the Examiner, and Applicants request that a copy of the published abstract for the priority application, PCT/US98/11753, be used. The text of that abstract is inserted herein.

B. Specification

The Examiner alleged that the specification does not accurately reflect the current co-pending status of the earlier filed application, SN 08/870,762. The first paragraph of the specification has been amended as suggested by the Examiner.

The Examiner also objected to the spacing of lines in Tables II through VII. Pages 32-34 and 36-39 of the specification as filed contain these tables and new pages incorporating spaced tables have been substituted for the original pages as suggested by the Examiner. No new matter is introduced by the substitution.

In view of the foregoing, Applicants respectfully request that the objections to the specification be withdrawn.

Applicants thank the Examiner for her reconsideration and withdrawal of the multiple grounds of rejection noted in Paper No. 6. Specifically, the Examiner withdrew (1) the rejection of claims 1 and 2 under 35 U.S.C. § 102(b) as allegedly anticipated by the Cooper *et al.* '014 patent or the Cooper *et al.* '841 patent, (2) the rejection of claims 1-3 under 35 U.S.C. § 102(e) as allegedly anticipated by the Rink *et al.* '106 patent, (3) the rejection of claims 1-10 under 35 U.S.C. § 103(a) as allegedly unpatentable over the Rink *et al.* '106 patent in view of the Gaeta *et al.* '411 patent, and (4) the rejection of claims 1-10 under 35 U.S.C. § 103(a) as allegedly unpatentable over Kolterman *et al.* (1996) or the Kolterman *et al.* '220 application or Moyes *et al.* (1996) or Thompson *et al.* (1997) in view of Cooper *et al.* (1989 abstract) and the Rink *et al.* '106 patent. The remaining grounds of objection and rejection are addressed below.

II. Rejections

A. 35 U.S.C. § 112, ¶ 1

The Examiner acknowledges that "Applicants have provided support in the instant specification and examples for a method of 'treating' obesity in a human subject comprising administering an effective amount of an amylin or an amylin agonist (see examples)," and concludes that claims to methods for treating obesity with an amylin or an amylin agonist are fully enabled within the meaning of 35 U.S.C. § 112. For reasons set forth in her August 4, 2000 Office Action, however, the Examiner rejected claims 1-10 as allegedly not enabled with respect to the claim term "preventing." The Examiner asserts that the specification "does not reasonably provide enablement for a method of preventing obesity in a human subject." *See* Office Action, August 4, 2000, Paper No. 3, page 3. The Examiner cites *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) and topically notes without further discussion the factors set out in that case, including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the art, the relative skill level within the art, the predictability or unpredictability of the art, and the breadth of the claims. Applicants respectfully traverse the rejection.

Those of ordinary skill understand that obesity exists in various degrees. Thus, the ability to prevent an escalation from one degree of obesity to a more severe degree of obesity with a pharmaceutical agent both treats an existing obese condition and prevents exacerbated or further obesity. Similarly, it is understood that use of such an agent provides the ability to prevent obesity in one who is in danger of manifesting the disease. The instant specification provides complete support for both treating and preventing obesity.

In recognition of the fact that various disease states can be both treated and prevented with a pharmaceutical compound, the U.S. Patent and Trademark Office has issued many patents over the years that contain claims to methods for "treating or preventing" various diseases. Such patents include, by way of example, U.S. Patent No. 6,274,608, issued on August 14, 2001, for "Compounds, their preparation and use." The '608 patent contains claims to compounds said to be useful in the treatment of conditions mediated by nuclear receptors, in particular the retinoid X receptor and the peroxisome proliferator-activated receptor families. It also contains claims to methods of "treating or preventing diabetes and/or obesity" using these compounds.

The person of ordinary skill would consider the detailed information found throughout the instant specification to be sufficient for the treatment and prevention of obesity. In addition to other pertinent disclosure, the specification at page 27 provides that effective doses of the compounds of the invention for preventing or treating obesity "will typically be in the range of about 0.01 to about 5 mg/day, preferably about 0.05 to about 2 mg/day and more preferably about 0.1 to 1 mg/day, for a 70 kg patient, administered in a single, divided or continuous doses." Page 28 of the specification also teaches that, "[p]referably, the doses of peptide agonists, for example, pramlintide, are administered subcutaneously in 30-300 μg doses given from one to four times a day, and more preferably from 30-120 μg doses given two to four times per day." The disclosure is supported with data from human clinical trials that shows the treatment of patients by lowering body weight *and the prevention of body weight increase*. See working Examples 1-3. Accordingly, methods of preventing obesity are fully taught, and carrying out the claimed invention in light of the specification does not require, as the Examiner has implied, "undue experimentation." Each of the *Wands* factors—the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the art, the relative skill level within the art, the predictability or unpredictability of the art—demonstrate that the invention is enabled for its full breadth. The Examiner has not provided any basis on which to believe that any of the *Wands* factors weighs against Applicants' claims that include preventing obesity.

As stated in *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971), a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented – as here – must be taken as in compliance with the enabling requirement of the first paragraph of Section 112, "unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." Indeed, "[A]ny party making the assertion that a U.S. patent specification or claims fails, for one reason or another, to comply with Section 112 bears the burden of persuasion in showing said lack of compliance." *Weil v. Fritz* , 601 F.2d 551, 555, 202 USPQ 447, 450 (CCPA 1979). Here, the Examiner has advanced no evidence other than the definition of "prevent" as recited in Webster's II New Riverside University Dictionary. Indeed, aside from a

reference to the "full scope" of the claims, the Examiner has not addressed any of pertinent factors in *Wands* and, Applicants respectfully submit, has otherwise failed to meet her burden of making a *prima facie* case.

For reasons set forth above, Applicants respectfully request that this rejection be reconsidered and withdrawn.

B. 35 U.S.C. § 103(a) [Claims 11-15] -- Kolterman *et al.* (1995) In View Of Rosenbloom *et al.* (1997), Rink *et al.* '367, and Morley *et al.* (1994)

The Examiner has rejected pending claims 11-15 as allegedly unpatentable under 35 U.S.C. § 103(a) over Kolterman *et al., Diabetes Care*, vol. 18, no. 8 (1995), in view of Rosenbloom *et al., Am. J. Dis. Child*, 131: 881-885 (1977), Rink *et al., WO 92/20367*, and Morley *et al., Am. J. Physiol.* 267:R178-R184 (1994). Applicants respectfully traverse. Claims 11-15 are directed to methods of reducing insulin-induced weight gain in human subjects using an amylin or an amylin agonist, and neither Kolterman *et al.* (1995) nor the alleged secondary references, alone or combined, teach or suggest reducing insulin-induced weight gain in human subjects using an amylin or an amylin agonist.

In order to establish a *prima facie* case of obviousness, the Examiner must demonstrate 1) a motivation to combine the alleged references in a manner that 2) teaches or suggests all of the claim limitations, and with 3) a reasonable expectation of success in making the specific combination claimed. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that alleged references may be combined or modified is not sufficient to establish a *prima facie* case of obviousness, and whether a claimed invention is believed to be within the capabilities of one of ordinary skill in the art is also not sufficient by itself to establish a *prima facie* case of obviousness. MPEP §2143.01. Obviousness cannot be established by combining the alleged teachings of the prior art to produce the claimed invention, absent some teaching suggestion or incentive supporting the combination. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984). Whether or not the claimed invention is "obvious to try" is irrelevant absent a reasonable expectation of success in the art as a whole at the time of filing for achieving what is claimed. *In re O'Farrell*, 853 F.2d 894, 903-904, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988).

The Federal Circuit has stated that "that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d at 998, 999 (Fed. Cir. 1999). Combining alleged prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time.").

Thus, a determination of obviousness cannot be based on the hindsight combination of components selectively culled from alleged prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way that they were combined by the inventor. *See Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc.*, 21 F.3d 1068, 1072, 30 USPQ2d 1377, 1379 (Fed. Cir. 1994) ("When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination."); *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 935, 15 USPQ2d 1321, 1324 (Fed. Cir. 1990) (the prior art must suggest to one of ordinary skill in the art the desirability of the claimed composition); *Interconnect Planning Corp.* v. Feil, 774 F.2d at 1143, 227 USPQ at 551. Evidence of "teaching away" must also be considered, as such teaching can completely undermine the necessary motivation to combine alleged references. *In Gambro Lundia AB v. Baxter Healthcare Corp.* 42 USPQ2d 1378, 1383 (Fed. Cir. 1997).

As noted above, the claims at issue relate to methods of "reducing insulin-induced weight gain in a human subject" by administering an amylin or an amylin agonist. As the Examiner points out, "Kolterman *et al.* are silent about . . . the effect of amylin or amylin agonist on weight gain." Kolterman *et al.* (1995) reports lowered postprandial hyperglycemia (elevated blood glucose) in human subjects with IDDM by an intravenous infusion of pramlintide ($^{25, 28, 29}$ Pro-h-

amylin). Kolterman *et al.* does not address insulin-induced weight gain, although it reports numerous other problems associated with hyperglycemia.

Kolterman *et al.* further focuses on a narrow time frame, five hours, over which time it would be next to impossible to gauge meaningful insulin-induced weight control (see, *e.g.*, Figures 1 and 2). Kolterman recognizes this and states that additional studies are necessary over an extended time period before meaningful inferences can be drawn beyond immediate acute effects: "[I]t needs to be demonstrated that similar results can be achieved throughout the entire day..." Kolterman (1995) at 1181, column 2, last ¶. Kolterman also teaches that amylin actions in rodent models are not necessarily indicative of amylin activities in humans: "This latter finding is consistent with recent observations in humans (9), but contradicts earlier observations in animal models (10-11)." (emphasis added). Because it involves extremely short time frames for application of [25, 28, 29] Pro-h-amylin, and moreover notes potential problems in applying these acute findings to humans, Kolterman is an unlikely reference to be combined with any other that pertains to the issue of weight gain.

The Examiner cites Rosenbloom *et al.* for the proposition that chronic insulin overdosage may be related to excessive appetite and weight gain in humans. At most, Rosenboom *et al.* suggests a reduction of insulin dosage. Discussion of insulin dosage would not suggest to one of ordinary skill in the art that an amylin or amylin agonist be used to treat obesity or insulin-induced weight gain in type 1 diabetics. Indeed, Rosenbloom does not even mention amylin or amylin agonists, and could not given the fact that the discovery of amylin at the Oxford University by Drs. Cooper and Willis was not reported until ten years later in the *Lancet* (August 1, p. 231-234 (1987)).

Rink *et al.* '367 fails to bridge the gap and, in fact, teaches away from Applicants' claimed invention by reporting that treatment with amylin likely has no useful effect on the weight of an animal:

> [A]pplicant believes that the appetite suppressant effects of amylin is seen only at very high doses and may be short lived. Indeed, applicant has discovered that in toxicological studies with amylin in both rats and dogs, where two weeks of amylin administration

were used, there was no reduction in food intake or weight in the animal.

Rink *et al.* '367, page 11; emphasis added.

Nor does Morley *et al.* bridge the gap. Morley *et al.* (1994) report the alleged modulation of food intake in mice with peripherally administered amylin. The Examiner states, among other things, that Morley *et al.* teach a method of "effectively suppressing or reducing food intake (i.e., treating obesity) . . . by administering up to 200 micrograms of amylin per kg." The Examiner references experiments in the paper comparing obese mice to lean mice treated with amylin. However, the relevant comparison, detailed in Morley's Experiment 3, is obese mice treated with amylin vs. obese control mice treated with saline. Two sets of experiments were done, at two dosage ranges. In the first, 50, 75, and 100 micrograms/kg of amylin were administered i.p. to ob/ob (obese) and ob/c (lean) mice, and food intake was observed. While differences between the obese and lean mice cohorts were observed, "[t]he interaction of drug dose and strain was not significant" (pg. R181, second column). In this first group, Morley found that "[a]mong the ob/ob mice, only the group treated with a 100 μg/kg dose of amylin significantly suppressed food relative to the control group for test periods of 0-30 and 0-60 min." However, this apparent result was negated by the second part of the experiment (which included an identical 100 ug/kg dose). In the second part of the experiment amylin was administered at 100, 150, and 200 μg/kg doses. Here again, differences could be seen between obese and lean mice, but "none of the saline vs amylin comparisons within strain was significant." The authors explain this lack of significance within obese or lean mice by noting that "control mice decreased food consumption . . . but amylin-treated mice continued at about the same amount" over the 60 minute time period (all quotes page R182). One of skill in the art reading this document would note that, compared to obese mice treated with saline, obese mice treated with amylin show no real difference in food intake. Although in the first part of Experiment 3, 100 μg/kg doses achieved statistical significance among obese mice, the very same dose and two higher doses in a second cohort showed no statistical significance on obese mice compared to lean controls. Thus, in view of these results over the course of this one hour experimentation, no conclusions about the effectiveness of amylin to treat obesity can be made. One of skill in the art would not be motivated to use amylin to treat or prevent obesity, not only in light of the inconclusive nature of these studies, but because the article would actually discourage one from pursuing such a course.

It reported that amylin treated mice actually ate for longer periods of time compared to saline treated controls (page R182, column 2 "Inspection of the data revealed that control mice decreased food consumption during this period, but amylin-treated mice continued to eat about the same amount as during the 0- to 30-min test period."). One would not conclude that an agent that contributed to persistent eating would be useful to treat or prevent obesity. Therefore, Morley *et al.* does not suggest, and in fact can be seen to teach away from, Applicants' claims.

Applicants note, furthermore, that the Morley *et al.* study is limited to 30 and 60 minute post-administration periods. It is submitted that such periods are too short to evaluate the utility of an agent for treatment or prevention of obesity. Morley *et al.* appear to acknowledge this in concluding, "[T]he answer to whether amylin is truly a physiological satiation agent will need to wait until amylin antagonists become available." R183, col. 2, paragraph 2. The patentability of the claims in light of Morley *et al.* is further underscored by the independent teachings of Kolterman *et al.*, discussed above, that rodent amylin models may not reliably predict activity in humans, and the teaching in Rink '367, also discussed above, that there is no appreciable reduction in food intake and weight reduction upon administration of amylin.

Accordingly, when taken as a whole, the art cited by the Examiner is silent or actually teaches away from the claimed invention, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

C. Double Patenting

The Examiner has provisionally rejected certain pending claims under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over the claims of co-pending application SN 09/870,762 (April 20, 2000 Office Action, Paper 6, ¶ 13). The Examiner has stated that although the pending claims are not identical to those in co-pending application SN 09/870,762, the claims are not patentably distinct from each other because of the overlapping scope of the claims.

The Examiner's rejection is unclear as to which, or all, of the pending claims have been rejected on these grounds. Applicants respectfully request the Examiner to clarify the rejection by identifying which pending claims have been provisionally rejected for alleged double

patenting. In light of the provisional nature of this rejection, Applicants further request that the Examiner hold this matter in abeyance until receipt of official notification of allowable claims in this and/or co-pending application SN 09/870,762, at which time, if necessary, Applicant will address a request for a terminal disclaimer.

D. 35 U.S.C. § 103(a) [claims 1-5] - Arnelo I or Arnelo II

The Examiner has rejected claims 1-5 under 35 U.S.C. § 103 (a) as allegedly unpatentable over Arnelo *et al.*, *Am. J. Physiol.* 271:6 pt 2:R1654-R1659 (1996) (Arnelo I), or Arnelo *et al., Scand J. Gastroenterol.* 31:83-89 (1996) (Arnelo II). The Examiner states, "The method of treatment of obesity is viewed as the same as the reduction in body weight in light of the experimental results presented in Example 1 of the instant specification." Applicants respectfully traverse and submit that the Examiner has failed to make a *prima facie* case of obviousness.

Arnelo I reports that the purpose behind the experiments described therein "was to investigate the dose-response effect of long-term administration of IAPP[1] on food intake and meal patterns in rats." Arnelo I at R1654, column 2. Arnelo I would not suggest to one of ordinary skill in the art any method of treating obesity in humans, as there was in fact no reported weight loss in Arnelo's experimental study on rats. Figure 4 of Arnelo I shows these rats consistently gained weight, even at the highest doses of administered IAPP. Weight gain is fundamentally inconsistent with a method of treating obesity, and thus Arnelo I does not teach or suggest the presently claimed methods of treating obesity and, if anything, teaches away from such use. Arnelo I further reports that the effects of chronic IAPP administration are "transient,"

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1 While Arnelo I state that IAPP and amylin are the same, Applicants note that one of the co-authors of Arnelo I, Per Westermark, previously reported and defined IAPP as a different molecule from amylin. Specifically, unlike amylin, IAPP was not defined as a 37 amino acid peptide having a C-terminal amide and disulfide bridge between amino acids at positions 2 and 7 of the peptide. *See* U.S. Patent No. 5,116,948, "Preparations of islet amyloid polypeptide (IAPP) and antibodies to IAPP," issued on May 26, 1992 to Westermark and Johnson. Thus, absent a specific indication that Westermark equates IAPP with the amylin discovery of Garth Cooper and Antony Willis (U.S. Patent No. 5,367,052, "Amylin Peptides") and actually used amylin and not his patented IAPP molecule, one of skill in the art would not have applied Westermark and Arnelo's teachings relating to IAPP to the amylin art.

which would further dissuade one of ordinary skill from contemplating its use for the treatment of obesity. *See, e.g.*, R1656, column 2, paragraph 4, bridging R1657.[2]

Arnelo II likewise only concerns the administration of IAPP in rats. Arnelo II report that, "Bolus injection or infusion of human IAPP did not inhibit food intake at any dose" and that suppression of feeding on administration of rat IAPP bolus injection and infusion effects had vanished by 24 hours at the 5 and 10 nmol/kg doses. Arnelo II, page 85, last paragraph. If the Arnelo II authors mistakenly referred to amylin as IAPP, and converting their nanomole doses to micrograms, these two ineffective dosages are both equivalent to over 1300 μg and 2700 μg doses in a 70 kg adult human. If such high doses were ineffective, one of ordinary skill art could not conclude that IAPP, let alone the amylins and amylin agonists claimed in the instant application, would be effective to treat human obesity.

Furthermore, although the chronic (*i.e.* continuous) administrations of IAPP reportedly decreased body weight in the initial portion of the Arnelo II experiment, by the sixth day of continuous infusion, the rats were increasing in body weight – once again demonstrating a temporal effect that is inconsistent with sustained weight control: "the reduced effect of IAPP with time during long-term exposure should be noted." Accordingly, one of ordinary skill in the art would not be motivated to apply the Arnelo II teachings to arrive at applicants' claimed invention.

Applicants respectfully request that this rejection be reconsidered and withdrawn.

E. 35 U.S.C. § 103 [Claims 6-8] – Arnelo I or II As Applied to Claim 5, Further In View of Bennett *et al.*

The Examiner has rejected claims 6-8 for alleged obviousness under 35 U.S.C § 103(a) over Arnelo I or Arnelo II as applied to pending claim 5, and further in view of Bennett *et al.*

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2 Arnelo I relates to continuous or "chronic" administration of IAPP. Arnelo I, at page R1657, column 2, teaches one of skill in the art that "it remains to be determined whether discontinuous modes of IAPP administration would produce less desensitization and marked effects on feeding."

(U.S. Patent No. 5,955,433, "Method of Thrombin Inhibition") (November 13, 2000 Office Action, ¶ 13). Applicants respectfully traverse.

The shortcomings of Arnelo I and II as applied to the law and claims 1-5 are discussed *supra*. Claim 6 recites administration of amylin or an amylin agonist from 1 to 4 times per day in dosage amounts of from 30 μg/dose to 300 μg/dose. Claim 7 depends from claim 6 and recites administration three times per day in an amount of about 60 ug/dose. Claim 8 also depends from claim 6 and recites administration four times per day in an amount of about 60 ug/dose. Although each of the Arnelo and Bennett documents is silent with respect to these particular claim features, the Examiner alleges that it would have been obvious to "arrive" at them by "routine experimentation or optimization." Obviousness is not established by mere conclusory statements. Under the law, even assuming *arguendo* that a combination of the cited documents is possible, the combination is insufficient as a matter of law to support a *prima facie* case of obviousness because all claim elements are not taught. Alleged prior art references or a combination of alleged references must teach or suggest all the limitations of the claims. *See In re Wilson*, 165 USPQ 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art."). The Examiner does not treat any of the alleged references either individually or as a whole in reciting a conclusion of obviousness.

Moreover, even assuming that all of the elements were present to combine, the teaching or suggestion to combine, as well as the expectation of success in doing so, must come from the prior art, not Applicants' disclosure. *See In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Here, the two groups of cited documents are directed to entirely different subject matter, with no motivational link existing between them. Bennett teaches methods and compositions for the treatment and diagnosis of diseases through modulation of expression of a nucleic acids encoding a platelet endothelial cell adhesion molecule-1. *See, e.g.*, Abstract. Arnelo I and II, by contrast, allegedly relate to a temporary reduction of weight in rats. The Examiner, who has the burden of establishing a *prima facie* case of obviousness within the meaning of 35 U.S.C. § 103, points to no motivation that would lead one of ordinary skill in the art to combine Bennett with either Arnelo document to arrive at the claimed invention. Further, to the extent that the Examiner cites Bennett for the proposition that human doses can be extrapolated from animal

studies, this generalization is inconsistent as applied to amylin in light of the above-described evidence in each of Kolterman *et al.*, Rink '367, and Arnelo I and II, that teaches away.

At best, the Examiner's rejection is predicated on an "obvious to try" rationale, the assertion being that one of the ordinary skill in the art would allegedly be motivated to experiment with a multitude of different dosage amounts and frequencies to arrive at Applicants' invention as defined in claims 6-8. This type of rejection has been deemed improper time and time again by the Federal Circuit: "'Obvious to try' has long been held not to constitute obviousness. A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 34 U.S.P.Q.2d 1210, *citing In re O'Farrell*, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988). The rejection fails, furthermore, because there is no base document which one might modify to "try" different dosages.

Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

F. 35 U.S.C. § 103(a) [claims 1-10] Kolterman *et al.* II in View of Meglasson

The Examiner has rejected claims 1-10 under 35 U.S.C. § 103(a) as allegedly unpatentable over Kolterman *et al.*, WO 96/4022 (Kolterman II) in view of Meglasson (U.S. Patent No. 5,134,164. Applicants respectfully traverse.

It is the law that any alleged reference "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097, 231 U.S.P.Q. 375, 380 (Fed. Cir. 1986). The law further provides that it is clear error to find obviousness where alleged references "diverge from and teach away from the invention at hand." *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

In general, Kolterman II relates to methods of lowering blood sugar in patients with type II diabetes mellitus who do not use insulin by administration of amylin agonists, in particular ^{25,28,29}Pro-h-amylin, which has been the subject of Phase I, II, and III clinical trials over the last

several years for treatment of diabetes. Kolterman II does not advocate to one of ordinary skill in the art that the presently claimed methods of treating obesity can be accomplished by the administration of an amylin or an amylin agonist. Indeed, the Examiner acknowledges on page 7 of the April 20, 2001 Office Action that "Kolterman *et al.* (II) do not expressly teach that their method is also useful in the treatment of obesity." Further, the Examiner has not set forth the basis on which one of ordinary skill in the art would conclude that the administration of amylin agonists in non-insulin-using Type 2 diabetes patients in Kolterman II are pertinent to the treatment of the obesity.

The Examiner claims that Meglasson stands broadly for the proposition that any compound useful in the treatment of hyperglycemia would also be useful in the treatment or prevention of obesity. However, the statement in Meglasson on which the Examiner relies does not support this conclusion. it reads as follows (emphasis added): "[A] compound that is useful in the treatment of hyperglycemia, impaired glucose tolerance, hyperinsulinemia, insulin insensitivity, hyperamylinemia, excess adiposity or hyperlipidemia could also be used to treat or prevent NIDDM, obesity, hypertension or atherosclerosis." Meglasson '164 patent, col. 2; lines 21-26 (emphasis added). Plainly, given that one of the diseases sought to be treated is hyperamylinemia (a condition characterized by excessive amylin in the blood), one of ordinary skill in the art surely would not understand amylin to be among Meglasson's proposed compounds because administering amylin would be expected to exacerbate this condition, not treat or prevent it. Accordingly, Meglasson teaches away from the invention, which is directed to the use of amylin or amylin agonists rather than to the treatment or prevention of excess levels of amylin.

In addition, Meglasson issued as a U.S. Patent on July 28, 1992 from a parent application filed February 28, 1990. The present application claims priority as a continuation-in-part to application Serial No. 08/870,762, filed June 6, 1997. Because a determination of non-obviousness is made from the reference point of one of ordinary skill in the art at the time the invention was made, whatever Meglasson 's teachings may have indicated to one of skill in the art in 1990 or 1992, by the time the present application was filed amylin and amylin agonists had never before been used or suggested to treat obesity in humans and additional studies by this time urged a different course of action. For example, Amylin Pharmaceuticals' U.S. Patent No.

5,280,014, issued January 18, 1994 (from an application filed July 18, 1991) and U.S. Patent No. 5,364,841, issued November 15, 1994 (from an application filed June 21, 1993) instructed the preferred use of amylin antagonists, *i.e.*, compounds that actually block the normal effects of amylin, to treat obesity. Importantly, these teachings were available to one of skill in the art after Meglasson, but before the present priority application was filed in 1997. In this regard alone, the Examiner has failed to take account of the whole of the art as it existed at the time of filing, including negative information that teaches away from the invention, and which is also considered proper evidence of the nonobviousness.

Also teaching away at the time is U.S. Patent No. 5,656,590, issued August 12, 1997 to Rink *et al.*, which claims priority to a PCT application filed on, and having a 35 U.S.C. § 102(e) date of, May 23, 1992. The Rink '590 patent describes and claims methods for the treatment of patients suffering from anorexia or a similar condition by administering an amylin or an amylin analogue in order to increase, not lose, weight.

Further, the Examiner cites column 2, lines 1-2 and 21-26 of Meglasson for the proposition that any compound that is useful in the treatment of hyperglycemia will be useful in the treatment of obesity. An examination of this passage in Meglasson, however, reveals that Meglasson did not, in fact, state this, and was not confident of such a general proposition, instead stating that such was merely possible. When considered as a whole with other art of the time, *e.g.*, the Rink *et al.* '590 patent and U.S. Patent Nos. 5,280,014 and 5,364,841, there was no clear motivation to do what Applicants claim and, in fact, doing so would have been considered improbable. Meglasson's statements should therefore be analyzed and confined to their proper context – the effect of the specific compound, 3-guanidinoproprionic acid, on obesity, and not the effect of any other glucose lowering compounds, including amylins and amylin agonists, on obesity. Meglasson does not even mention amylin.

Thus, in contrast to the Examiner's conclusion that it would have been obvious to use an amylin agonist to treat obesity, when taken as a whole in the relevant time frame the collective art teaches the opposite. One of ordinary skill in the art would not have been motivated to use the available amylin agonists for methods of treating obesity.

Accordingly, Applicants respectfully request that this rejection also be reconsidered and withdrawn.

G. **35 U.S.C. § 103(a) [claims 1 and 5] over Morley *et al.***

The Examiner has rejected claims 1 and 5 under 35 U.S.C. § 103(a) over Morley *et al.*, *Am. J. Physiol.* 267:R178-R184 (1994). These claims are directed to methods of treating or preventing obesity in a human subject by administering an amylin or an amylin agonist (claim 1) from one to four times per day (claim 5). The Examiner asserts that Morley *et al.* teaches (1) the suppression of food intake in obese, lean and diabetic mice, (2) that amylin is a peripheral satiety agent, and (3) that the obese mouse is a classical genetic model of obesity. From this, the Examiner concludes that it would have been obvious to "produce the instant invention by extending Morley's [animal experimentation] to humans for the expected benefit of reducing the incidence of obesity in humans, as treating obesity in humans is highly desired in the art." Applicants respectfully traverse the Examiner's rejection.

A determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor. *See Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc.*, 21 F.3d 1068, 1072, 30 USPQ2d 1377, 1379 (Fed. Cir. 1994) ("When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination."). However, it is the law that any alleged reference "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097, 231 U.S.P.Q. 375, 380 (Fed. Cir. 1986). The law further provides that it is clear error to find obviousness where alleged references "diverge from and teach away from the invention at hand." *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Evidence of "teaching away" must be considered, and such teaching can completely undermine

the necessary motivation to combine references. *In Gambro Lundia AB v. Baxter Healthcare Corp.* 42 USPQ2d 1378, 1383 (Fed. Cir. 1997).

As demonstrated in section II.B, above, the experiments in Morley *et al.* are not conclusive. One of skill in the art would not be motivated to use amylin to treat or prevent obesity in humans in light of the inconclusive nature of these studies in mice. Morley *et al.* would actually discourage one from pursuing such a course because it showed that amylin treated mice actually ate for longer periods of time compared to saline treated controls: "Inspection of the data revealed that control mice decreased food consumption during this period, but amylin-treated mice continued to eat about the same amount as during the 0- to 30-min test period." Morley *et al.*, R182, column 2 (emphasis added). Given this, one would not predict from a short-term experiment in mice that an agent that contributed to persistent eating would be an anti-obesity treatment. Therefore, Morley *et al.* does not suggest, and in fact teaches away from, Applicants' claims.

The Examiner's position is further unsound in light of the teaching in Kolterman I, discussed *supra*, that rodent amylin models are not predictive of activity in humans, and Rink '367, discussed *supra*, that amylin administered to rodents had no appreciable reduction in food intake and weight reduction. When the art of the time is considered as a whole, there is plainly insufficient motivation to do what Applicants describe and claim. Even Morley *et al.* questioned the predictability of their studies for future experiments and applications: "The studies reported here are pharmacological in nature. Although they help to elucidate a potential role for amylin in physiology, the answer to whether amylin is truly a physiological satiety agent will need to wait until amylin antagonists become available." Morley at R183, column 2, ¶ 2 (emphasis added). Adding to the confusion and further negating the Examiner's contention that sufficient motivation existed to do what Applicants claim, by the time the present application was filed, U.S. Patent Nos. 5,280,014 and 5,364,841 instructed the preferred use of amylin antagonists, *i.e.*, compounds that actually block the normal effects of amylin, to treat obesity. The instant claims, by contrast, are directed to amylin and amylin agonists.

Accordingly, viewed in its entirety and in light of the knowledge in the art the Morley data would not suggest to one of ordinary skill in the art at the time of filing the instant

application that it would be obvious to use an amylin or amylin agonist to treat or prevent obesity in humans, and Applicants respectfully request that this ground of rejection be withdrawn.

H. The Additional Documents Cited By the Examiner But Not Relied Upon

The Examiner has cited, but not relied upon, numerous other documents that she alleges are "relevant prior art." *See* Office Action, April 20, 2001, Paper 6, page 9, ¶ 18. Applicants do not accede to this characterization and reserve the right to traverse should the Examiner seek to rely upon one or more of these documents in determining the patentability of the claims of this application.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance, and seek an early notice to that effect. Should the Examiner have any remaining questions, she is encouraged to telephone the undersigned so that they may be promptly resolved.

Respectfully submitted,

Dated: 8/20/01

By: _____
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Table II

Body Weight: Changes from Baseline
Weights at Weeks 13, 26, and 52

Time Point/Body Weight (kg)	Placebo (N=154)	Pramlintide 30 or 60 μg QID (N=163)
Baseline		
Mean (SE)	76.5 (1.1)	76.4 (1.1)
Median	75.1	75.9
Range	45,125.7	46.4, 113.6
Week 13 (3 Months)		
Mean (SE)	76.5 (1.1)	75.4 (1.1)
Median	75.1	75.6
Range	45,125.7	47.3, 110.5
Change from Baseline		
Mean (SE)	0.2 (0.2)	-1.0 (0.2)
Median	0	-1.0
Range	-6.0, 8.2	-7.6, 8.2
Hodges-Lehman Estimator for Difference from Placebo	-	-1.2
p-value †	-	0.0001*
Week 26 (6 Months)		
Mean (SE)	76.9 (1.1)	75.5 (1.1)
Median	75.9	76.4
Range	45.8, 126.8	46.4, 111.2
Change from Baseline		
Mean (SE)	0.6 (0.2)	-0.9 (0.3)
Median	0.55	-0.5
Range	-7.3, 9.3	-23.5, 9.1